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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Brian Seed et al.	Art Unit:	1644
Serial No.:	08/756,018	Examiner:	G. Ewoldt
Filed:	November 25, 1996	Customer No.:	21559
Title:	P-SELECTIN LIGANDS AND RELATED MOLECULES AND METHODS		

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REPLY TO NOTIFICATION OF NON-COMPLIANCE

WITH 37 C.F.R. § 1.192(c)

In reply to the Notification of Non-compliance mailed July 17, 2003, Appellants submit herewith three copies of a substitute Appeal Brief. As required by the Examiner, Appellants have deleted, from page 14, the reference to:

(i) Alon *et al.*, Distinct cell surface ligands mediate T lymphocyte attachment and rolling on P and E selectin under physiological flow. *J. Cell. Biol.*, 127:1485-

1495, 1994;

(ii) Goetz *et al.*, Dynamics of neutrophil rolling over stimulated endothelium in vitro. *Biophys. J.*, 66:2202-9, 1994;

(iii) Ley *et al.*, Sialylated O-glycans and L-selectin sequentially mediate myeloid cell rolling in vivo. *Blood*, 85:3727-3735, 1995; and

(iv) Schmuke *et al.*, A method for measuring leukocyte rolling on the selectins. *Anal. Biochem.* 226:197-201, 1995, has been deleted from page 14.

Applicants respectfully submit that the substitute Appeal Brief is in compliance with 37 C.F.R. § 1.192.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: August 15, 2003

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APPELLANTS' BRIEF ON APPEAL SUBMITTED PURSUANT TO 37 C.F.R. § 1.192

In support of Appellants' Notice of Appeal that was filed in the above-captioned case on May 31, 2002, of the Examiner's final rejection mailed on December 7, 2001, submitted herewith in triplicate is Appellants' Brief on Appeal.

TABLE OF CONTENTS

Real Party in Interest

The real party in interest is The General Hospital Corporation, to whom all interest in the present application has been assigned. (Reel 8437, Frame 0899).

Related Appeals and Interferences

There are no currently pending appeals or interferences related to this case.

Status of Claims

Claims 1-9, 11, and 15-23 are canceled.

Claims 10, 12-14, and 24-25 are currently pending.

Claims 10, 12-14, and 24-25 were rejected in a Final Office Action mailed on December 7, 2001, and are appealed.

Status of Amendments

All amendments have been entered.

Summary of the Invention

Applicants have discovered that it is possible to create artificial P-selectin ligands by combining amino acid sequences containing tyrosine sulfation sites with sialyl Le^x addition sites. These sites may originate in different polypeptides and be inserted into a third, carrier polypeptide, or the sites may originate from the same polypeptide and be repositioned relative to one another. Generally, the claimed invention features purified nucleic acids encoding such artificial P-selectin ligand polypeptides that contain a tyrosine sulfation site and a sialyl Le^x addition site, wherein at least one of the sites is located at an amino acid position where it does not naturally occur. The invention also features vectors and cells containing the claimed nucleic acids.

Issues

This appeal presents two issues:

1. Whether the Examiner erred in rejecting claims 10, 12-14, and 24-25 under 35 U.S.C. § 112, first paragraph, for lack of enablement.

2. Whether the Examiner erred in rejecting claims 10, 12-14, and 24-25 under 35 U.S.C. § 112, first paragraph, for inadequate written description.

Grouping of Claims

The claims do not stand or fall together because they are different in scope and are drawn to different genera of synthetic P-selectin ligands having different descriptions. On both issues presented above, however, the grouping of claims is the same.

Group 1

Claims 10 and 12-14 stand or fall together because they are drawn to, or incorporate, nucleic acids encoding a polypeptide that contains (i) an N-linked sialyl Le^x addition site, and (ii) a tyrosine sulfation site.

Group 2

Claim 24 stands alone because it is drawn to nucleic acids encoding a polypeptide that contains (i) an N-linked sialyl Le^x addition site, and (ii) the tyrosine sulfation site of Factor VIII set forth in SEQ ID NO: 15.

Group 3

Claim 25 stands alone because it is drawn to nucleic acids encoding a polypeptide that contains (i) Ile135 through Ser225 of the CD43 precursor sequence, and (ii) a tyrosine sulfation site.

Argument

Issue 1: Rejection of Claims 10, 12-14, and 24-25 for Lack of Enablement

The Patent Office has the initial burden to establish a reasonable basis to question enablement. In *In re Marzocchi*, 439 F.2d 220, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971), the court stated:

> a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

The M.P.E.P. (§ 2164.04) echoes the holding of *Marzocchi*:

> (I)t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise there would be no need for the Appellant to go to the trouble and expense of supporting his presumptively accurate disclosure.

Claims 10, 12-14, and 24-25 were finally rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement on two grounds. First, the Examiner asserts that (Paper 34, Final Office Action mailed December 7, 2001, page 3):

> Applicants' disclosure of a single polypeptide in support of the broad genus encompassed by Claim 10 is insufficient support that additional polypeptides could be made without undue experimentation

because

> the disclosure is insufficient to support the instant claims to an invention that would encompass an essentially unlimited number of polypeptides.

Second, the Examiner, after pointing out that the specification discloses experimental results from *in vitro* assays while the intended uses are *in vivo* and, recognizing that working examples are not a criterion for patentability, asserts that "some sort of *in vivo* enablement is required." The Examiner argues that:

> the specification fails to establish sufficient correlation between said assay and any *in vivo* process, thus, said assay can not be considered a relevant *in vitro* model for any *in vivo* process.

Applicants respectfully disagree with these grounds of rejection and submit that the Examiner has failed to rebut the presumption that Applicants' disclosure is accurate and enabling.

A Large Genus Does Not Prima Facie Lack Enablement

The Examiner asserts that undue experimentation is required to practice the claimed invention because there are "an essentially unlimited number of tyrosine sulfation sites" resulting in the claims encompassing an "essentially unlimited number of polypeptides." The Examiner also asserts that Applicants have not addressed the problem of the positioning of the sialyl Le^x addition sites and tyrosine sulfation sites in relation to one another. These assertions are in error.

Tyrosine Sulfation Sites

The standard for enablement is articulated in *In re Wands* 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). In defining the boundaries of undue experimentation, the *Wands* court stated that "the key word is 'undue' not 'experimentation'" and that "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine." *Id.* at 737.

In asserting this argument, the Examiner has improperly concluded that the disclosure must not be enabling because the size of the claimed genus is large. Specifically, the Examiner asserts that the number of possible tyrosine sulfation sites is "essentially unlimited." Applicants respectfully disagree and first point out that, regardless of the size of a claimed genus, a disclosure is enabling if an artisan is able to practice the full scope of that genus.

As discussed in Applicants' Reply of September 20, 2001, and reasserted here, the characteristics of tyrosine sulfation sites were well recognized in the art at the time of application filing. A skilled artisan would have no trouble in making and using such sites in a synthetic P-selectin ligand. For example, Hortin *et al.* (*Biochem. Biophys. Res. Comm.*, 141:326-333, 1986) and Huttner (*Annu. Rev. Physiol.*, 50:363-376, 1988) had extensively characterized the requirements for tyrosine sulfation. Hortin *et al.* state (page 331):

> Based on the foregoing analysis of amino acid sequences surrounding sulfation sites, **five simple rules** were

empirically derived to aid in predicting the location of sites of sulfation. Tyrosine residues that are likely sites of sulfation are identified by the following criteria:
1) There is an acidic residue at position -1 or -2,
2) There are at least 3 acidic amino acid residues within 5 residues (positions -5 to +5) of the tyrosine residue,
3) No more than 1 basic amino acid residue are within 5 residues of the tyrosine,
4) No more than 3 hydrophobic residues (Ile, Leu, Phe, and Val) are within 5 residues of the tyrosine,
5) No cysteine residues are within 15 residues of the tyrosine.

Hortin makes it clear that there are ten critical amino acids, other than the tyrosine, which comprise a sulfation site (criteria 1-4). Although one can "imagine" a large number of ten amino acid combinations, a formulaic application of the "five simple rules" will immediately provide the artisan with an expectation of success or failure. The "trial-and-error" in tyrosine sulfation site design is carried out largely by testing a proposed amino acid sequence against the "five simple rules" and eliminating those which do not conform.

Further, Applicants provide the artisan with several tyrosine sulfation sites to use intact, or as a starting point for further modification. Specifically, Applicants provide extensive characterization of the tyrosine sulfation site of PSGL-1 (see, Specification page 21, line 11 through page 23, line 14). Applicants also identify the tyrosine sulfation site of coagulation Factor VIII (SEQ ID NO: 15). Thus, using Applicants' disclosure and information known in the art at the time of filing, synthetic tyrosine sulfation sites and P-selectin ligands could be designed with a high expectation

of success before ever entering the laboratory. The only experimentation remaining is routine screening to determine the effectiveness of the synthetic P-selectin ligand, assays for which are provided in Applicants' specification at page 13, line 11 through page 16, line 4. Applicants respectfully submit that, regardless of the number of possibilities, the design of tyrosine sulfation sites does not require undue experimentation.

Of course, this ground of rejection is moot insofar as applies to claim 24 (Group 2) because the claim specifically recites the tyrosine sulfation site of Factor VIII provided in SEQ ID NO: 15. Thus, claim 24 does not encompass a "genus" of tyrosine sulfation sites.

Positioning of the Sialyl Le^x Addition Site and Tyrosine Sulfation Site

The Examiner further asserts that "Applicant has not addressed the problem of positioning said sialyl Le^x addition sites and tyrosine sulfation sites in relation to one another." This assertion is clearly incorrect and does not support the enablement rejection.

As noted previously (Reply of September 20, 2001), part of Applicants' inventive contribution is the recognition that, for a synthetic P-selectin ligand, the relationship (conformation and distance) between the tyrosine sulfation site and the sialyl Le^x site is more flexible than previously thought. Applicants' disclosure demonstrates that non-naturally occurring P-selectin binding molecules can be made without strictly

inserting a naturally occurring P-selectin recognition site. Thus, Applicants have demonstrated that greater flexibility for designing artificial proteins exists.

Further, contrary to the Examiner's assertion, Applicants provide guidance on the relative positioning and intervening sequence requirements between the tyrosine sulfation and sialyl Le^x sites. For example, in Figure 3, Applicants demonstrate that fusion of the N-terminal domain of PSGL-1, containing the tyrosine sulfation site, facilitates P-selectin binding activity in chimeric molecules having a sialyl Le^x site derived from any of CD43, CD34, or GlyCAM-1. These experiments show that the P-selectin binding is tolerant of considerable sequence variability in the region linking the tyrosine sulfation and the sialyl Le^x sites. Applicants also constructed mutant PSGL molecules by varying the number of repeated elements. This has the effect of altering the spacing between the tyrosine sulfation and the sialyl Le^x sites. Figure 4 of Applicants' specification demonstrates that P-selectin binding function is maintained despite considerable deletion of the repeated elements in PSGL. As shown in Figure 4B, deletion of 1-3 repeated elements did not appreciable affect P-selectin binding, and mutants having a deletion of 4-8 elements retained approximately 75% of the native binding activity. Thus, contrary to the Examiner's assertion, Applicants have addressed the problem of positioning of the sialyl Le^x and the tyrosine sulfation sites relative to one another and have presented this information in their specification.

Working Examples

Finally, on this issue, Applicants wish to address the Examiner's incorrect assertion that Applicants provide only a single working example (Figure 13) in the specification. To the contrary, in addition to the HL-60 cell rolling assay (described in more detail below), Applicants demonstrate the P-selectin binding activity of synthetic P-selectin ligands. For example, Figure 3B shows that COS cells expressing a synthetic P-selectin ligand that is a chimera of PSGL-1 and either CD43 or CD34 possess P-selectin binding activity equal to COS cells expressing native PSGL-1. And a chimera of PSGL-1 and GlyCAM-1 is shown to impart a binding activity of approximately 50% compared to native PSGL-1.

The results presented in Figure 4 also constitute a working example of the claimed nucleic acids. Specifically, the nucleic acids encoding the PSGL-1 deletion mutants of Figure 4 fall within the scope of claim 10 because the encoded polypeptides contain both an N-linked sialyl Le^x addition site and a tyrosine sulfation site wherein at least one of the sites is located at a non-naturally occurring position. As described above, several of these deletion mutants demonstrate P-selectin binding activities that are equivalent to native PSGL-1.

Finally, in Figure 15 of the specification, Applicants show that COS cells expressing a chimera of CD43 and Factor VIII also have a high level of P-selectin binding activity. Thus, contrary to the Examiner's assertion, Applicants have provided more than a single working example. Applicants have, in fact, made a significant

showing of data in the form of working examples which enable the artisan to fully practice the claimed invention.

The Specification is Enabling for In Vivo Uses

As a second basis for the enablement rejection, the Examiner asserts that the specification discloses *in vitro* assay results but "the only specific disclosed intended uses are *in vivo*." The Examiner further states that (Paper 34: Final Office Action of December 7, 2001; page 3, last sentence):

> the specification fails to establish sufficient correlation between said assay and any *in vivo* process, thus, said assay can not be considered a relevant *in vitro* model for any *in vivo* process.

Applicants respectfully disagree as this conclusion is in error.

As noted previously, the Federal Circuit and the Patent Office provide Applicants with the presumption that a disclosure is enabling. *In re Marzocchi*, 439 F.2d 220, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971); M.P.E.P. § 2164.04. The Examiner is required to explain why he doubts the truth or accuracy of any statement in a supporting disclosure and to back up those assertions with acceptable evidence or reasoning which is inconsistent with the contested statement. In the present case, the Examiner has done nothing other than provide an unsubstantiated conclusory statement of doubt. Nowhere does the Examiner provide evidence or reasoning by which he arrives at this conclusion.

The M.P.E.P. § 2164.02 sets forth the requirements for enablement with regard to working examples. In relevant part, § 2164.02 states:

> An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention.
>
> *****
>
> In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate.
>
> *****
>
> A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739, 747 (Fed. Cir. 1985).

Thus, the M.P.E.P. recognizes that *in vitro* assays can support claims to *in vivo* utilities if there is a correlation between the assay and the *in vivo* condition. The M.P.E.P. also notes that the specification alone need not establish the correlation provided that a correlation was known at the time of application filing.

The Federal Circuit recognizes the position articulated in M.P.E.P. § 2164.02, that claims to *in vivo* applications may be supported by experimental results from *in vitro* assay systems. The court in *In re Brana,* 51 F.3d 1560. 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) reversed a U.S.P.T.O. decision that *in vitro* activity did not support therapeutic applications *in vivo*. The appellants in *In re Brana* used *in vitro* data from two lymphocytic leukemia cell lines to support claims to *in vivo* uses of chemotherapeutic agents. Similarly, Applicants demonstrate *in vitro* efficacy of

synthetic P-selectin ligands using an HL-60 (human leukemia cell line) cell rolling assay (Figure 13 and page 15) to support *in vitro* diagnostic and *in vivo* therapeutic uses. Thus, Applicants' claims do not lack enablement, *per se*, because no *in vivo* animal or human testing data is disclosed.

The HL-60 cell rolling assay correlates with *in vivo* inflammatory processes and is sufficient to support *in vivo* utilities for the synthetic P-selectin ligands of the invention. The correlation between leukocyte rolling and the inflammatory process *in vivo* were well documented in the art at the time of filing. For example, Kubes *et al.* state (*J. Immunol.*, 152:3570-3577, 1994, first paragraph, first sentence; emphasis added; art of record):

> The movement of leukocytes from the main stream of blood to afflicted tissue is a key feature of inflammation. This process consists of at least two distinct events: 1) the initial contact between the leukocyte and endothelium described as leukocyte rolling and 2) firm or stationary adhesion.

The art also identifies both *in vitro* and *in vivo* rolling assays using various leukocyte cell types, including the HL-60 promyelocytes used by Applicants. These rolling assays were recognized and used as a reliable indicator and investigational tool for the early stages of the inflammatory process.

The law is well settled that *in vitro* assay results can support claims to *in vivo* utilities provided that there is a reasonable correlation between the two. Both the specification and the prior art understood that the process of leukocyte rolling is an

integral part of the inflammatory process *in vivo*. *In vitro* cell rolling assays generally, and the HL-60 cell rolling assay used by Applicants, were recognized as useful surrogates for investigating *in vivo* inflammatory processes. As the Examiner has provided no evidence to the contrary, Applicants respectfully submit that there is a strong correlation between the *in vitro* HL-60 rolling assay and the *in vivo* inflammatory process. Accordingly, the results provided in the specification constitute working examples and provide the artisan with a reasonable expectation of success in using the synthetic P-selectin ligands of this invention.

Summary

In view of the above, Applicants submit that the present specification enables the skilled artisan to make and use the synthetic P-selectin ligands encoded by the nucleic acids of the present invention. In view of Applicants' disclosure, the artisan is able to recognize, create, and modify both the tyrosine sulfation sites and sialyl Le^x addition sites, as well as alter the spacing between the two, with a reasonable expectation of retaining P-selectin binding. Further, Applicants' demonstration that synthetic P-selectin ligands block HL-60 rolling provides an expectation that these ligands will be successful as diagnostics and therapeutics for *in vitro* or *in vivo* use. Accordingly, the rejection of claims 10, 12-14, and 24-25 for lack of enablement should be reversed.

Issue 2: Rejection of Claims 10, 12-14, and 24-25 for Inadequate Written Description

In asserting this rejection, the Examiner states that

> [t]he specification discloses no limitation on the sites which might comprise either a "sialyl Le^x addition site" or a "tyrosine sulfation site". Absent any disclosed limitations, a "sialyl Le^x addition site" must be considered to be any amino acid capable of accepting either an O-linked or N-linked carbohydrate addition. Similarly, a "tyrosine sulfation site" must be considered to be any tyrosine. Paper 32: Office Action of March 21, 2001, page 4.

Applicants respectfully disagree and point out that, for the reasons discussed previously, a tyrosine sulfation site is not any tyrosine, nor is a sialyl Le^x addition site any amino acid capable of accepting either an O-linked or N-linked carbohydrate addition. Applicants also note that, contrary to the Examiner's assertion, more than a single functional example of each of these sites is disclosed.

The Federal Circuit, in *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1569, provide for fulfillment of the written description requirement either through the enumeration of a plurality of species or by "other appropriate language." As an alternative to reciting a large number of species falling within a claimed genus, the *Lilly* court specifically provides for "a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." *Id.* at 1569.

Applicants respectfully submit that ample guidance and description is provided by the specification or was known in the art at the time of filing to provide an adequate written description of the claimed invention.

Sialyl Le^x Addition Sites

Contrary to the Examiner's assertion, a sialyl Le^x addition site cannot be "any amino acid capable of accepting either an O-linked or N-linked carbohydrate addition." Applicants point out that claim 10 is limited, in relevant part, to nucleic acids encoding polypeptides containing N-linked sialyl Le^x addition sites. The specification describes N-linked glycan addition as occurring at the consensus site of N X S/T, wherein N is asparagine, S is serine, T is threonine, and X is any amino acid except proline. Specification at page 25, lines 20-22. Applicants also provide other guidance for creating and identifying sialyl Le^x addition sites. For example, Figure 10 identifies at least five sites for N-linked glycan addition in IgG1. Further guidance is provided in the specification at page 25, line 22 through page 26, line 17. Preferable sites are present or created in the CH2 region of an immunoglobulin molecule, are located on the outside of the immunoglobulin molecule, or are located in a region which is minimally disruptive to the primary and secondary structure of the protein. Thus, an artisan is clearly apprised of the structural features of a sialyl Le^x addition site and where such sites should be created.

Moreover, this ground of rejection is moot insofar as it applies to claim 25 (Group 3) because the claim specifically recites the nucleic acids encoding a polypeptide

containing Ile135 through Ser225 of the CD43 precursor sequence (SEQ ID NO: 17). The sialyl Le^x addition site recited in claim 25 is therefore explicitly described.

Tyrosine Sulfation Sites

The Examiner is also incorrect in asserting that "a tyrosine sulfation site must be considered to be any tyrosine." As discussed previously, sulfation occurs at tyrosines that are contained within sequences of a very specific character and for which tests are available in the art. Further, Applicants provide several examples of tyrosine sulfation sites useful in creating the synthetic P-selectin ligands of this invention. For example, Figure 14 describes the tyrosine sulfation site of coagulation Factor VIII and the fourth component of human complement. Additionally, Applicants demonstrate the tolerance of the PSGL-1 sulfation site to modification. In Figure 9 and the accompanying text at page 22, line 7 through page 23, line 4, Applicants provide experimental data on the biological effects of altering the tyrosine sulfation site. Specifically, Applicants demonstrate that conversion of the tyrosines to phenylalanines results in the complete loss of P-selectin binding, whereas replacement of the threonine residues with alanine reduced but did not abolish binding activity. Thus, the specification and the prior art clearly describe tyrosine sulfation sites.

In addition, this ground of rejection is moot insofar as it applies to claim 24 (Group 2) because the claim specifies nucleic acids encoding a polypeptide that contains

the tyrosine sulfation site of Factor VIII as provided in SEQ ID NO: 15. The tyrosine sulfation site recited in claim 24 is, therefore, explicitly described.

Positioning of the Sialyl Le^x Addition Site and Tyrosine Sulfation Site

For the reasons discussed previously, Applicants submit that the relative positioning of the sialyl Le^x addition site and tyrosine sulfation site is adequately described in the specification. Specifically, in Figure 4, Applicants describe the production and biological activity of PSGL mutants with altered spacing between these two sites. Site spacing was altered by deleting a varying number of the repeated elements of PSGL. Additionally, Applicants describe artificial P-selectin ligands that are combinations of sialyl Le^x addition sites and tyrosine sulfation sites derived from different molecules (see, for example, Figure 3). These synthetic ligands also have varied spacing between the two sites. Applicants submit that, on the issue of the spacing between the sialyl Le^x addition site and tyrosine sulfation site, the genus of synthetic P-selectin ligands encoded by the claimed nucleic acids is adequately described in the specification.

Summary

Applicants respectfully submit that the specification clearly describes sialyl Le^x addition sites, tyrosine sulfation sites, and their spacing in artificial P-selectin ligands. Contrary to the Examiner's assertion, neither of these sites encompasses an unlimited

number of possibilities. Accordingly, the rejection of claims 10, 12-14, and 24-25 for inadequate written description should be reversed.

Conclusion

Appellants respectfully request that the rejections of claims 10, 12-14, and 24-25 be reversed. No fee is believed due at this time.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: August 15, 2003

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Appendix of Claims on Appeal

10. A purified nucleic acid encoding a polypeptide that is a synthetic P-selectin ligand, wherein said polypeptide contains an N-linked sialyl Le^x addition site and a tyrosine sulfation site, and wherein at least one of the sites is located at an amino acid position in said polypeptide which is different from its position in a naturally-occurring P-selectin ligand.

12. The purified nucleic acid of claim 10, wherein said nucleic acid further encodes an antibody or antibody fusion protein.

13. A vector comprising the nucleic acid of claim 10.

14. A cell comprising the nucleic acid of claim 10.

24. The purified nucleic acid of claim 10, wherein said tyrosine sulfation site consists of the Factor VIII tyrosine sulfation sequence set forth in SEQ ID NO: 15.

25. The purified nucleic acid of claim 10, wherein said polypeptide comprises Ile135 through Ser225 of the CD43 precursor sequence (SEQ ID NO: 17).